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Vitamin D in schizophrenia and depression: a clinical review

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Summary

Evidence from pre-clinical and clinical studies support a role for vitamin D in many mental disorders. In this review, we discuss the role of vitamin D in the aetiology and treatment of schizophrenia and depression and their physical health comorbidities. Although observational studies support a potential association between vitamin D and schizophrenia and depression, sufficient high quality evidence from clinical trials does not yet exist to establish a place for vitamin D supplementation in optimising clinical response or promoting physical health. Completed randomised controlled trials are needed to provide insights into the efficacy and safety of vitamin D in the management of mental disorders.

Keywords: psychosis; mood disorders; cholecalciferol

Learning objectives:

After reading this article the reader will:

Understand the epidemiology of vitamin D deficiency in schizophrenia

Understand the associations of vitamin D with schizophrenia and depression

Awareness of how to assess, and consider treatment for vitamin D deficiency

Introduction

Vitamin D is a secosteroid hormone, recognised as a neuroprotective factor with a role to play in brain development (Harms 2008, Eyles 2013). Vitamin D promotes neurodevelopment, with a range of actions such as promoting cell growth and differentiation, regulation of neurotransmission, immunomodulation and with antioxidant and anti-inflammatory effects.

Vitamin D deficiency has been associated with a range of mental disorders including mood disorders, psychotic disorders, autism and cognitive decline.

Vitamin D physiology

Vitamin D belongs to a group of fat-soluble vitamins. Its primary functions are to aid the intestinal absorption of calcium and phosphate, and on bone

mineralisation (Holick 2013). The two main forms of vitamin D are: vitamin D3 or cholecalciferol, which is formed in the skin after exposure to sunlight and ergocalciferol, and vitamin D2, which is obtained by irradiation of plants or plant materials or foods.

Vitamin D levels are influenced by environment and lifestyle. Endogenous synthesis following cutaneous exposure to ultraviolet B radiation is the primary source (see Figure 1). A smaller proportion is acquired from dietary sources. It is not a widely appreciated fact, but nutritional sources of vitamin D are relatively limited (Holick 2013). Recently a large meta genome-wide association study (GWAS) involving 31 studies with a total of 79,366 individuals identified genetic variants at three loci (group component (GC), 7-dehydrocholesterol reductase (NADSYN1/DHCR7), and 25-hydroxylase (CYP2R1)) influencing vitamin D levels (Jiang 2018), though the findings were suggestive of a relatively small heritability rate for vitamin D levels indicating that modifiable environmental factors are the main determinant of vitamin D levels.

INSERT FIGURE 1

UV sunlight stimulation will depend on the season of the year, latitude and skin exposure. Vitamin D levels thus vary seasonally, with deficiency more common in winter and at higher latitudes, reflecting ambient levels of sunlight (Hypponen and Power 2007) as well as in urban settings due to lifestyle choices and lower sunlight exposure (Holick 1995). People with more pigmented skin need more sunlight to produce vitamin D, so are particularly affected by limited sun exposure; lower levels of vitamin D are consistently observed in Black and Asian populations (Ford 2006). Older age is associated with lower vitamin D levels, with reduced sunlight exposure and decreased ability to synthesize vitamin D cutaneously with sunlight exposure contributing factors.

Vitamin D deficiency- epidemiology

Vitamin D deficiency is a global problem; more than a billion people worldwide are believed to have suboptimal levels (Holick and Chen 2008). A recent systematic review of 195 studies including 168,000 people from 44 countries identified that 37% had mean 25-hydroxyvitamin D (25(OH)D) concentrations lower than <50nmol/L (equivalent to <20ng/ml). Additionally, 6.7% had 25(OH)D levels below 25 nmol/L (equivalent to <10ng/ml), corresponding to vitamin D deficiency, while only 11% had 25(OH)D levels above 75 nmol/L (equivalent to >30ng/ml), the level classed as sufficient (Hilger 2014).

Classification of vitamin D status

Serum levels of the main circulating form of Vitamin D, 25-hydroxyvitamin D (25(OH)D), are usually taken as a proxy of vitamin D status (Ross 2011, Holick and Chen 2008), as it is a more stable compound than the physiologically active form, 1,25(OH)₂D₃, with higher serum concentrations and a longer half-life (approximately 20 days compared to 7 hours) (Lips 2007).

Controversy remains about what vitamin D levels are optimal or sufficient. The definitions of sufficiency above are based on observations relating to 25(OH)D's role in calcium homeostasis and optimal calcium absorption. Parathyroid hormone (PTH) levels decline with reducing concentrations of 25(OH)D, although this decline plateaus and reaches a nadir at 25(OH)D concentrations of 75-100nmol/L (30-40ng/ml) (Holick 2007). Intestinal calcium absorption is optimal at concentrations >80nmol/L (equivalent to 32ng/ml) (Holick and Chen 2008). The definition of vitamin D sufficiency of >50nmol/L 25(OH)D, is based on the observation that PTH levels normalise with 25(OH)D concentrations of >50nmol/L (Ross 2011), with similar levels are required to prevent osteomalacia and to ensure optimal bone function (Ebeling 2014).

Likewise, variable definitions of vitamin D deficiency have been used. Most commonly, 25(OH)D concentrations of <50nmol/L (20ng/ml) have been taken to indicate deficiency, while concentrations of 51-74nmol/L (21-29ng/ml) indicate insufficiency (Holick and Chen 2008). A more conservative definition of Vitamin D deficiency provided by the International Osteoporosis

Foundation, is serum 25(OH)D concentrations $<25\text{nmol/L}$ ($<10\text{ng/ml}$), with insufficiency defined as $25\text{-}50\text{nmol/L}$ ($10\text{-}20\text{ng/ml}$) (Dawson-Hughes 2010). The US Institute of Medicine (IOM) recommend that vitamin D levels $>20\text{ng/ml}$ ($>50\text{nmol/L}$) are recommended to optimise skeletal benefits, based on trials in the general population (Ross 2011). Most recently, the Endocrine Society clinical guidelines based on studies of people at high risk for vitamin D deficiency recommend that a concentration of 25(OH)D $>30\text{ng/ml}$ ($>75\text{nmol/L}$) be attained to improve outcomes (Holick 2011).

Vitamin D and depression

Research exploring the relationship between suboptimal vitamin D and depression risk has provided inconsistent findings. Several narrative reviews, assessing the association between low vitamin D and depression suggest an inconclusive relationship.

A systematic review and meta-analysis of observational studies concluded that vitamin D levels were inversely associated with the prevalence of depression (Anglin 2013). However, the observational nature of the included studies precluded drawing conclusions on a causal relationship (Anglin 2013).

There remains a paucity of longitudinal data investigating the relationship between vitamin D and depression. The few existing studies have provided inconclusive results. A recent large-scale population based study of 3251 adults older than 55 investigating long-term associations between vitamin D serum levels and depression identified a cross sectional association between low vitamin and depression, but found no evidence for a longitudinal relationship (Jovanova 2017). The cross sectional relationship might be expected, as people who are depressed may be less able to engage in outdoor activity and may limit their sun exposure. However, if vitamin D is a risk factor for depression, then we would expect to find that vitamin D concentrations had a longitudinal association with depression and depressive symptoms, which was not found in this study (Jovanova 2017). This replicated previous longitudinal data which failed to identify a longitudinal association between low vitamin D and depression (Chan 2011, Toffanello 2014), though

was contradictory to findings from two other longitudinal studies(May 2010, Milaneschi 2010), which identified a relationship between suboptimal vitamin D levels and the prospective onset of depression.

A meta-analysis of RCTs of vitamin D supplementation as a treatment for depression identified six RCTs with 1203 participants (72% females) including 71 depressed patients (five trials included participants at risk of depression and one trial included patients with depression). There was no significant effect of vitamin D supplementation on depression scores ((standardized mean difference = -0.14, 95% confidence interval =-0.41 to 0.13, $P = .32$; odds ratio =0.93, 95% confidence interval =0.54 to 1.59, $P = .79$)(Li 2014). Both these systematic reviews(Anglin 2013, Li 2014) supported the conclusion of previous narrative reviews indicating that no clear causal relationship between suboptimal vitamin D and depression has been identified.

Vitamin D augmentation in depression-trials

Only one small randomised double blind trial of vitamin D3 augmentation of a specific antidepressant medication in depressive disorder has taken place. Over an eight week period there was a significant improvement in depressive symptoms in those whose fluoxetine 20mg daily was augmented with 1500IU of vitamin D 3 (n=20) compared to placebo (n=20)(Khoraminy 2013). A controlled open label trial of antidepressant (any) augmentation with a single oral dose of 300,000IU of vitamin D 3 (n=24) showed a significant improvement in depressive symptoms over a 4 week period in comparison to antidepressant alone use (n=15)(Zanetidou 2011). Over 90% of the included cases treated with vitamin D3 augmentation had a 25(OH)D level <75nmol/L (<30ng/ml). A later RCT showed efficacy for a single dose of 300,000 IU intramuscular vitamin D (n=40) in improving depressive symptoms at 8 weeks following a single injection compared to placebo (n=40), an effect not seen with the lower 150,000 IU dose (n=40)(Mozaffari-Khosravi 2013).

An RCT of 78 people aged 60 and older in receipt of treatment for depression, identified a non significant change in the mean depression score between

those treated with 50,000 IU of vitamin D3 weekly for 8 weeks compared to those treated with placebo (although the mean vitamin D level (22.57 ± 6.2 ng/ml) in the treatment group may be considered to have been optimal)(Alavi 2018). An earlier double blind RCT of 50,000 IU vitamin D weekly compared with placebo found a non-significant decrease in depressive symptoms over an 8 week period (Sepehrmanesh 2016). A double blind RCT of dialysis patients with depression did not identify a significant reduction in depressive symptoms at following treatment with 50,000 IU vitamin D weekly for 52 weeks ($n=362$)(Wang 2016).

Vitamin D and bipolar depression

There has been a single RCT of vitamin D3 augmentation in bipolar depression, with no significant difference in depression symptom scores between those treated with 5000 IU of vitamin D3 daily ($n=16$) and placebo ($n=17$) after 12 weeks (Marsh 2017). This was despite a significantly higher mean increase in vitamin D levels in the augmentation group (9.9 (8.2) ng/ml) compared to the placebo group (1.3 ± 4.3 ng/ml).

The RCTs to date in mood disorders have been limited by small sample sizes, heterogeneity of study populations and vitamin D dosing techniques. These trials have produced inconsistent findings, which provide at best a mild signal for a beneficial effect of vitamin D on mood, but which is far from conclusive.

Vitamin D supplementation and impact on depression symptom scores and mental health

In addition to trials of vitamin D as a therapeutic agent in depression, RCTs have investigated the vitamin D as a preventative agent. A few RCTs have investigated vitamin D supplementation in improving depressive symptoms or depression scale scores, and those that have done so, had inconsistent findings; some showing a positive effect(Jorde 2008, Khoraminy 2013), while others finding no significant association(Kjaergaard 2012, Yalamanchili and Gallagher 2012, Vieth 2004). There was no association with improved depression and anxiety symptom scores in a cohort of young healthy adults supplemented with 5000 IU of vitamin D3 for 6 weeks compared to

placebo(Dean 2011), though there was a low prevalence of vitamin D deficiency in the test population. A randomised trial of vitamin D supplementation with 800 IU/day in women aged 70 or more did not identify any significant improvement in mental health outcomes with vitamin D3 supplementation, though the study was limited by a low level of depression in the study sample and the moderately low dose of vitamin D3 supplementation (Dumville 2006). A randomised trial investigating the effect of low dose (600 IU) and high dose (4000 IU) vitamin D 3 daily use (total n=82), found significant improvements in well being for those treated with high dose therapy at 6 months follow up (Vieth 2004) . Other randomised trials have found benefits with vitamin D supplementation in seasonal affective disorder (n=8 treated with 100,000 IU of vitamin D and n=7 treated with phototherapy) (Gloth 1999), and in improving depressive symptom scores in overweight or obese patients (BMI> 28kg/m²) treated with 20,000 IU of vitamin D3 twice weekly compared to placebo (cases were not vitamin D deficient nor were they depressed) (Jorde 2008).

These studies have not always focused on patients with clinical depression or vitamin D deficiency, rather they have involved vitamin D3 supplementation in general population samples, thus limiting interpretation of the findings, and contributing to inconclusiveness of findings. These studies are further limited by being underpowered, with small sample sizes, and heterogeneous study populations.

Vitamin D and psychotic disorders

Vitamin D insufficiency is highly prevalent in people with schizophrenia and other psychotic disorders (Suetani 2017). In a cross sectional study of 324 community based people with established psychosis, 86% had suboptimal vitamin D levels (<50ng/ml). In a systematic review, 63% met criteria for Vitamin D deficiency (with the threshold level to define deficiency ranging from 10-40 ng/ml)(Adamson 2017).

We identified that vitamin D levels are lower at the first episode of psychosis than in matched healthy controls (Crews 2013), and that 80% (n=134) of FEP cases have suboptimal vitamin D levels at time of first contact with services (Lally 2018). Lifestyle and physical health factors associated with an increased risk of vitamin D insufficiency or deficiency such as smoking, increased body mass index, social withdrawal and inactivity resulting in decreased sunlight exposure, are all more frequent in people with psychotic disorders.

Epidemiological studies have indicated that those born in late winter/early spring (Davies 2003), at higher latitudes (Saha 2006) and in urban settings have an increased risk of schizophrenia, leading to suggestions that this risk may be mediated by vitamin D deficiency. This association is further suggested by the increased rate of psychosis in Black African or Black Caribbean migrant populations where vitamin D is low. Cross sectional data in FEP and established psychosis has identified lower mean Vitamin D levels in those of Black African or Caribbean ethnicity compared to white populations (Lally 2018, Lally 2016), though whether this might differentially impact on clinical symptoms or symptomatic response to treatment has not been investigated. Prenatal vitamin D deficiency has been hypothesised to impact on fetal neural development thus increasing the risk of schizophrenia (McGrath 1999). This possibility is supported by a Danish longitudinal case-control study which showed that vitamin D status in neonates was associated with the risk of schizophrenia (McGrath 2010) and by a birth cohort study demonstrating an increased risk of schizophrenia in Finnish males not given vitamin D supplements during the first year of life (McGrath 2004).

Vitamin D3 supplementation in schizophrenia

The only randomised trial to date in schizophrenia investigating vitamin D3 augmentation was conducted in a population of clozapine treated patients with treatment resistant schizophrenia (all with vitamin D level <30ng/ml). At 8 weeks, there was no significant difference in psychotic symptoms between those treated with 14,000 IU per week of vitamin D3 (n=24) compared to

placebo (n=23), though a signal towards improved cognitive performance relating to attention and recall was detected (Krivoy 2017).

Vitamin D and clinical symptoms in FEP

A major limitation of work so far in FEP is the cross sectional design of most studies, limiting any inference of a causal relationship between vitamin D and clinical status-it may as easily be that the relationship identified between symptoms and low vitamin D, be it in acute psychotic episodes (Yuksel 2014), or in FEP (Graham 2015), may be the result of, rather than a cause of psychosis or depression.

We recently investigated the longitudinal relationship between vitamin D levels at time of first contact with services in FEP and clinical symptoms at 12 months, identifying a significant association between higher vitamin D levels at first contact for psychosis and lower negative symptoms and total psychotic symptoms at 12 month follow up(Lally 2018). This is the first longitudinal assessment of vitamin D levels and associations with psychotic symptoms.

Vitamin D is considered to be neuroprotective, and is postulated to have brain antioxidant properties, reducing oxidative stress (Wrzosek 2013, Nerhus 2016, Mitra 2017) by decreasing the production of the oxidant nitric oxide (Garcion 2002), and increasing the production of antioxidants such as glutathione (Garcion 1996, Wrzosek 2013). Previous studies have hypothesised that unmitigated oxidative stress can contribute to the development of negative symptoms through a dysregulation of glutamate-GABA excitatory-inhibitory responses (Sullivan and O'Donnell 2012, Albayrak 2013), while higher glutamate levels in the anterior cingulate cortex have been associated with increased negative symptoms in First Episode Schizophrenia (Egerton 2012). Vitamin D's anti-inflammatory properties are supported by the finding that vitamin D supplementation can reduce levels of C-reactive protein (CRP), a marker of inflammation (Chen 2014). This is mirrored in established psychosis In which an inverse relationship between vitamin D and CRP levels has been identified (Lally 2016).

Vitamin D and physical health in psychotic disorders

Vitamin D and cardiometabolic risk in psychotic disorders

Higher vitamin D levels have been associated with improved longer term clinical outcomes, with observational studies showing inverse associations of circulating 25-hydroxyvitamin D with risks of death due to cardiovascular disease and cancer (Chowdhury 2014). However, there is as yet no consistent evidence for routine supplementation.

To date, epidemiological evidence concerning the association between vitamin D and cardiometabolic risk factors in community dwelling individuals with established psychotic illnesses is limited. For the first time in a population with established psychosis, we identified that those with the highest levels of vitamin D have a lower prevalence of MetS (20.5 %), compared to those in the lowest (39.1 %), second (48.3 %) and third quartile (43.1 %) of vitamin D (all $p < 0.01$)(Lally 2016). This was the first large scale study to have identified an association between decreased 25(OH)D levels and cardiovascular risk factors in psychotic illnesses. Of interest, we identified associations with hypertension and low 25(OH)D levels, which may be a causally related finding. This is suggested by findings in the general population where low 25(OH)D levels are associated with a higher risk of incident cardiovascular disease and specifically hypertension(Wang 2008). The strongest correlations with low 25(OH)D levels were with factors related to high body fat(Lally 2016) , which is supported by the findings that those with increased adipose tissue stores (in which vitamin D, being fat soluble, is stored) due to obesity, have lower circulating levels of vitamin D due to this increased storage capacity(Wortsman 2000).

Vitamin D and bone mineral density (BMD) in psychosis

Osteoporosis is two and half times more common in schizophrenia compared to controls, with 52% having low bone mass (Stubbs 2014) and significantly reduced bone mineral density at the lumbar spine(Gomez 2016).

Only three studies to date have assessed associations between vitamin D and bone mineral density in schizophrenia (Rey-Sanchez 2009, Bergemann 2008, Hallahan 2008). In the cross sectional study of Hallahan et al, 15 patients with chronic schizophrenia, resident in a long stay residential unit, had BMD measures recorded by DEXA scan. There were no significant correlations between vitamin D levels (mean 23.8nmol/L (SD=8.9) nmol/L and BMD(Hallahan 2008). The Rey-Sanchez et al case-control study measured BMD using quantitative ultrasound (QUS) in 73 people with schizophrenia (males =48), who were all treated with antipsychotics. There was no significant correlation between vitamin D levels (mean 25(OH)D level: females: 20.4 (SD=26.1) ng/mL (equivalent to 51.0nmol/L); males: 15.1(12.0)ng/ml (equivalent to 37.8nmol/L)) and phalangeal BMD values; though a significant negative correlation between the PTH and lower bone mass was identified in males and females ($r = 0.347$, $p < 0.05$)(Rey-Sanchez 2009). In the case control study of Bergemann et al., 72 premenopausal women with schizophrenia (mean age 33.8 years (SD=6.5 years, range 20.5–45.3 years] were matched to 71 age- and sex-matched healthy controls. Those with schizophrenia had no significant difference in BMD (T-score) compared to controls. Those with schizophrenia had a significantly reduced mean 25(OH)D concentration of 16.3 (SD=7.9) ng/ml compared to controls 24.6 (SD=11.5) ng/ml (<0.001), though no significant correlation between serum 25(OH)D levels and BMD were reported in the patient group(Bergemann 2008). If an individual with schizophrenia has a history of fragility fractures, or evidence of reduced bone mineral density or osteoporosis, then supplementary calcium and vitamin D should be prescribed as in the general population(Aspray 2014), along with any direct treatments for osteoporosis where indicated.

Managing vitamin D deficiency in psychotic disorders: do we know when to screen and treat?

Given the variation the definition of vitamin D deficiency, in the UK, Public Health England recommend the use of vitamin D supplementation (400 IU/day) for all in winter/autumn months, with year round supplementation

advised for those with darker skin pigmentation. Meanwhile, the National Osteoporosis Society has set the following serum 25(OH)D thresholds: “<30 nmol/l (12ng/ml) is deficient; 30–50 nmol/l (12-20ng/ml) may be inadequate in some people; >50 nmol/l (>20ng/ml) is sufficient for almost the whole population” (Aspray 2014). What does this mean for the clinical care of people with schizophrenia? Should we test all patients for vitamin D deficiency? How should we interpret test results and what treatment might be considered? The answer is that we do not yet know whether and how to adapt the general population advice for use in people with psychosis.

It is more likely than not that a person with established psychosis will have suboptimal vitamin D levels(Lally 2016), and a pragmatic approach is reasonable when considering vitamin D testing- as in high risk general population groups, a presumptive diagnosis of insufficiency could be made, based on risk factors, without the need for (expensive) testing of vitamin D levels unless symptomatic(Aspray 2014).

It is perhaps most appropriate to measure vitamin D levels in summer or autumn, where a secular trend towards more optimal vitamin D levels will be seen. It is reasonable to consider people with schizophrenia and bipolar affective disorder as a high-risk group for suboptimal vitamin D levels. The National Osteoporosis Society recommend that such patients, as a minimum, should be treated with lifestyle advice and over the counter vitamin D supplements at a dose of 400 IU/day (Aspray 2014). If the vitamin D level is measured and is < 30nmol/L (<12ng/ml), then consideration for correction should be made, with a loading dose of 40,000 IU of colecalciferol given orally weekly for 7 weeks and vitamin D levels rechecked at 12 weeks to allow the level to plateau. If levels are now sufficient (i.e. >50nmol/L (>20ng/ml), then a maintenance dose of oral colecalciferol 800-2000 IU/day should be initiated, alongside dietary advice and engagement in outdoor activity. A similar maintenance regimen is advised for people with vitamin D insufficiency (30-50nmol/L (12-20 ng/ml)(Aspray 2014).

Lifestyle advice should be offered to all patients, and education that the best source for vitamin D is sensible levels of sunlight exposure. Spending 10-15

minutes in the sunlight on most days of a week, with face and arms exposed, will suffice to ensure adequate vitamin D levels(Nowson 2012).

Discussion

Vitamin D deficiency is associated with psychotic disorders, and with depression, as well as with many other chronic physical conditions. The question remains whether vitamin D is a causal factor or a consequence of these illnesses. Over 90% of people with established psychosis have suboptimal vitamin D levels, but depression rates in psychotic disorders are not that high, nor are persisting psychotic symptoms universally prevalent(Lally 2017). The observed associations could be due to reverse causation, the illness affecting the vitamin D levels, although our recent prospective paper, while requiring replication, opens the possibility of a direct effect of vitamin D levels on outcomes in early psychosis(Lally 2018) . The evidence that vitamin D deficiency in early life may be a risk factor for later psychosis is somewhat stronger(Eyles 2018). It may be the case that vitamin D when suboptimal is no longer neuroprotective perhaps due to the loss of its antioxidant or anti-inflammatory effects, leaving the person more vulnerable to emerging illnesses, such as psychosis or depression. In terms of supplementation, randomised trials fail to indicate symptom improvements with vitamin D augmentation in schizophrenia and depression. Nevertheless, vitamin D testing and supplementation has crept into routine medical practice, with the assumption that optimization of vitamin D levels will have longer-term benefits for physical health. However evidence for this is lacking, even in the general population (Manson 2019).

Conclusion

Vitamin D deficiency has been associated with poorer mental health, depression and with psychotic disorders, as well as with chronic physical conditions. However, the evidence base establishing vitamin D as a potential cause rather than consequence of depression is lacking, with some evidence that developmental vitamin D deficiency may be pertinent to psychosis risk.

Well-designed clinical trials are needed to further study the relationship between repletion of vitamin D stores and clinical outcomes in patients with depression and schizophrenia before routine testing and supplementation can be recommended. In the meantime, the guidelines for the general population should be followed, bearing in mind that the risks of vitamin D deficiency in those with psychosis and depression are higher than in the general population.

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